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Alkane Hydroxylation by a Nonheme Iron Catalyst that Challenges the Heme Paradigm for Oxygenase Action

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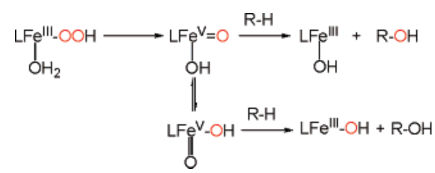
Selective oxidation of hydrocarbons under mild conditions constitutes a major challenge of modern chemistry.[1] Nonheme iron enzymes, such as methane monooxygenase[2] and Rieske dioxygenases,[3] catalyze such reactions and have inspired the development of synthetic models as alkane oxidation catalysts.[4] Exceptional nonheme iron catalysts are those containing tetradentate N_4 ligands belonging to the tripodal TPA and linear BPMEN family that can perform efficient stereospecific alkane hydroxylation using H_2O_2 as oxidant.[4] These bioinspired catalysts have provided key insights into the mechanisms by which alkanes are oxidized by enzymes. The common mechanism invoked in these studies follows the heme paradigm[5] in which a high-valent iron-oxo species first abstracts a H atom from a substrate C−H bond and the incipient alkyl radical then rebounds with the nascent Fe−OH moiety to form the product C−O bond (Scheme 1).[2,4] Labeling studies indicate that the O atom introduced into the substrate C−H bond derives mainly from the H_2O_2 oxidant. However, a minor fraction incorporates an O atom from water into the product, which is explained by oxo-hydroxo tautomerism of the high-valent HO−Fe═O oxidant.[5,6] Herein we describe a new remarkably efficient nonheme iron catalyst in the stereospecific oxidation of alkanes using H_2O_2 as oxidant that yields alcohol products with an unexpectedly large fraction of their oxygen atoms derived from water. This unprecedented result challenges the established heme paradigm and sheds new light into how nonheme iron centers may differ from heme centers in their mode of oxidative action.

Iron complex $[Fe^{II}(CF_3SO_3)_2(^{Me2}PyTACN)]$ (**1**) (see Figure 1) was prepared and structurally characterized (for details, see Supporting Information). Its crystal structure presents a distorted octahedral iron(II) center having a tetradentate ^{Me2}PyTACN ligand and two triflate anions coordinated *cis* to each other.

Complex **1** is a very efficient catalyst for the hydroxylation of cyclohexane by H_2O_2. When 10 equiv of H_2O_2 were delivered by syringe pump together with 1000 equiv of water, 6.0 turnover numbers (TN) of cyclohexanol (*A*) and 0.5 TN of cyclohexanone (*K*) ($A/K = 12$) were obtained, corresponding to a 65% efficiency in the conversion of H_2O_2 into products. Both efficiency and *A*/*K* selectivity exhibited by **1** were comparable to values reported for $[Fe^{II}(BPMEN)(CH_3CN)_2]^{2+}$ (63% yield and $A/K = 8$), considered the prototypical example of an efficient stereospecific alkane hydroxylation catalyst.[4b] Additional evidence implicated a metal-based oxidant rather than HO•. The intermolecular kinetic isotope effect evaluated in the hydroxylation of a 1:3 molar mixture of cyclohexane and its deutero-analogue was 4.3. In addition, **1** oxidized adamantane with a large 3°/2° normalized selectivity (30). Last, the oxidation of *cis*-1,2-dimethylcyclohexane (*cis*-DMCH) afforded the tertiary alcohol product with 93% retention of configuration. Overall, these characteristics are consistent with those of some previously described nonheme iron complexes.[4]

Scheme 1



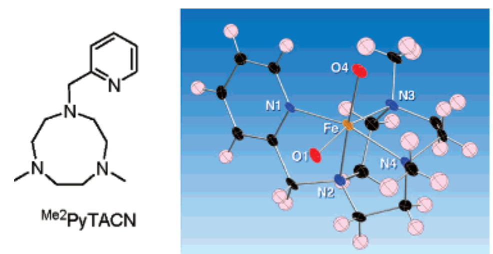


Figure 1. Left: schematic representation of the ligand. Right: thermal ellipsoid plot (50% probability) of **1**; triflate ligands (except for the O atoms bound to Fe) are omitted for clarity.

Interestingly, ^{18}O-labeling experiments in the hydroxylation of different alkanes catalyzed by **1** revealed intriguing differences between this catalyst and previously reported nonheme N_4Fe systems. The oxidation of cyclohexane by **1** with 10 equiv of $H_2{}^{18}O_2$ in the presence of 1000 equiv of $H_2{}^{16}O$ afforded 47% ^{18}O-labeled cyclohexanol. Complementary experiments with 10 equiv of H_2O_2 and 1000 equiv of $H_2{}^{18}O$ yielded 42(3)% ^{18}O-labeled cyclohexanol. The same levels of label incorporation from $H_2{}^{18}O$ were observed in the hydroxylation of cyclooctane (Table 1). This level of oxygen incorporation from water was the highest for any synthetic nonheme catalyst thus far. Furthermore, when oxidations of cyclohexane were carried out with different $H_2{}^{18}O$ concentrations, the fraction of ^{18}O-labeled cyclohexanol (% $R^{18}OH$) increased linearly with the amount of $H_2{}^{18}O$ at lower $H_2{}^{18}O$ concentrations, but plateaued at 42(3)% at higher concentrations (Figure S2), suggesting the involvement of a water binding pre-equilibrium, as precedented for Fe(TPA).[4b] These results support the mechanism shown in Scheme 1 proposed for Fe(TPA) and Fe(BPMEN) catalysts in which a $HO{-}Fe^V{=}O$ oxidant is formed via water-assisted heterolysis of the O−O bond of a $H_2O{-}Fe^{III}{-}OOH$ intermediate.[4b,7] If complete oxo-hydroxo tautomerism[5,6] of the $HO{-}Fe^V{=}O$ moiety occurred, a maximum value of 50% would be expected for the amount of labeled water incorporated into the alcohol product. The $H_2{}^{18}O$-labeling results described above clearly approach this maximum, so that the C−O bond that is formed can be made with either the oxygen from H_2O_2 or the oxygen from H_2O with almost equal probability.

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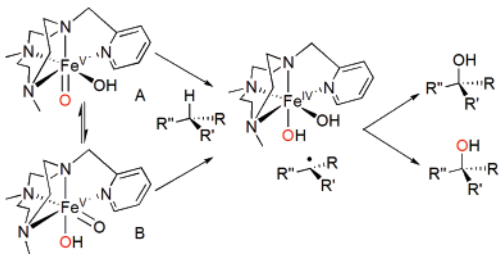
Table 1. Percentage of ^{18}O Incorporation into Alcohol Products by Fe(L) Catalysts in the Presence of 1000 equiv of $H_2{}^{18}O$

substrate	^{Me2}PyTACN	TPA[4b]
cyclohexane	42	29
cyclohexane-d_{12}	40	35
cyclooctane	44	23
cis-DMCH (3° C−H)	79	6
adamantane (3° C−H)	74	6
2,3-dimethylbutane	76	

Scheme 2



Surprisingly, even higher levels of $H_2{}^{18}O$ incorporation (76 ± 3%) were obtained for alcohol products in the oxidation of alkanes with tertiary C−H bonds, such as adamantane, *cis*-DMCH, and 2,3-dimethylbutane. Furthermore, this unexpectedly large value was found to be independent of substrate concentration (25−1000 mM). This observation strongly implicates the HO−Fe^V═O species as the only oxidant capable of alkane oxidation in the case of **1**.

The labeling results for **1** differ significantly from those reported for Fe(TPA) (Table 1). For the latter catalyst, label incorporation from $H_2{}^{18}O$ into substrates with 2° C−H bonds decreased with the C−H bond strength and labeling of 2°-ol products was much higher than for 3°-ol products. These results suggested that C−H bond cleavage and oxo-hydroxo tautomerism were competitive processes, as also found for iron porphyrin complexes.[4b,5,6] However, this was not the case for **1** since higher water incorporation was observed in the oxidation of the weaker 3° C−H bonds, and this level of incorporation was independent of *cis*-DMCH concentration. To rationalize the high level of label incorporation, we considered the possibility that a carbocation intermediate was formed and subsequently trapped by water, but discarded it because of the high retention of configuration observed for *cis*-DMCH hydroxylation. We also considered the possibility that the HO−Fe^V═O oxidant became doubly labeled by rapid, multiple intermolecular exchanges with $H_2{}^{18}O$, but rejected it on the basis of a $H_2{}^{18}O$-labeling experiment where cyclohexane and *cis*-DMCH were oxidized in competition with each other. *cis*-DMCH reacted much faster than cyclohexane, and so should have a shorter lived oxidant. Nevertheless, the 3°-ol thus formed contained 74% label from water, while cyclohexanol contained only 38%. Thus, the difference in label incorporation cannot be determined by how much ^{18}O is present in the common Fe^V oxidant, and a modified mechanistic scenario is required for **1**.

In Scheme 2, we propose a scenario in which the structure of the substrate can play a role in determining the course of C−O bond formation. For **1**, the two Fe^V(O)(OH) isomers (**A** and **B**) in equilibrium via oxo-hydroxo tautomerism are distinct since the ligands *trans* to the oxo and hydroxo groups are not chemically equivalent and the orientations of the pyridine ligand relative to the Fe═O bond are different. No matter which isomer abstracts the H atom from substrate, a common $Fe^{IV}(OH)_2$ species is formed. The *cis* configuration of the two hydroxo groups differs from the *trans* configuration required in heme complexes and is a unique feature of these nonheme iron catalysts. Thus, the alkyl radical can in principle rebound with either OH group, the outcome of which determines the %$H_2{}^{18}O$ incorporation. Given that these values range from 40% for cyclohexane-d_{12} to 79% for *cis*-DMCH, the energy difference between the two possible rebound trajectories is <2 kcal mol^{-1}, which is consistent with DFT calculations.[8] Thus, the labeling results indicate that 2°-alkyl radicals do not discriminate between the two OH groups, but 3°-alkyl radicals favor rebound with the OH group derived from water. Perusal of the structure of **1** (Figure 1) suggests steric effects may provide a possible rationale for this preference since the hemisphere surrounding O1 is less sterically congested.

In conclusion, **1** is an efficient alkane hydroxylation catalyst that can incorporate surprisingly large amounts of water into products via an unusual rebound-like mechanism. A similar mechanism may be operating in the hydroxylation of indane to 1-indanol by toluene or naphthalene dioxygenase to account for the high level of $H_2{}^{18}O$ incorporation (68%) found.[9] In addition, the α-ketoglutarate-dependent halogenases represent an established biological example in which C−H bond cleavage initiated by an Fe═O moiety is consummated by rebound not with the incipient OH group but with the adjacent halide ligand.[10] Thus, **1** may serve as a model for this unusual enzymatic chemistry, which suggests that a broader mechanistic landscape than in heme systems applies to nonheme sites.

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Supporting Information Available: Experimental procedures for the preparation of **1** and for the oxidation reactions and the cif file for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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